respiratory depressant effects occurred following 3290W93 administration than was observed following fentanyl administration.

REMARKS

Submission of Substitute Drawings

In the November 29, 2001 Notice to File Corrected Application Papers, the Office rejected the drawings for containing excessive text and required submission of substitute drawings.

In response, the applicants are submitting substitute Figures 1A, 1B, 2A, and 2B to replace the rejected Figures 1 and 2 as originally filed. In such substitute drawings, the text following the figure numbers has been removed, and appropriate descriptive legends have been added, as suggested by the Office in the Notice to File Corrected Application Papers.

The applicants hereby state that the substitute drawings contain only minor formality changes as described hereinabove, and no new matter is introduced in such substitute drawings. The Office is respectfully requested to review the substitute drawings submitted herewith, and upon approval of the same, to replace the originally filed Figures 1 and 2 with the substitute drawings.

Amendment of the Specification

Corresponding to the changes made in the substitute drawings, applicants have amended the instant specification.

Specifically, the applicants have changed the figure numbers in the specification, in accordance with those of the substitute drawings, and have added a new section for "Brief Description of the Drawings".

Amendment of the Abstract

In the November 29, 2001 Notice to File Corrected Application Papers, the Office objected to the Abstract for containing more than 150 words.

In response, the applicants have hereby amended the Abstract to reduce the number of words therein to less than 150.

The applicants respectfully request the Office to enter this Amendment before proceeding with further examination of the present application.

Respectfully submitted,

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APPENDIX A

Version with Markings to Show Changes Made In the Specification

1. On page 13, new paragraphs have been added after line 15.

2. On page 66, the paragraph beginning at line 4 has been changed, as follows:

As an indication of respiratory depression, blood CO_2 levels were observed to increase as a result of alfenta administration. The key finding in the experiment, however, was that BW373U86 dose dependently reduced the level of pCO_2 seen following the alfenta infusion. Results are depicted in [Fig. 1] Figures 1A and 1B.

3. On page 66, the paragraph beginning at line 9 has been changed, as follows:

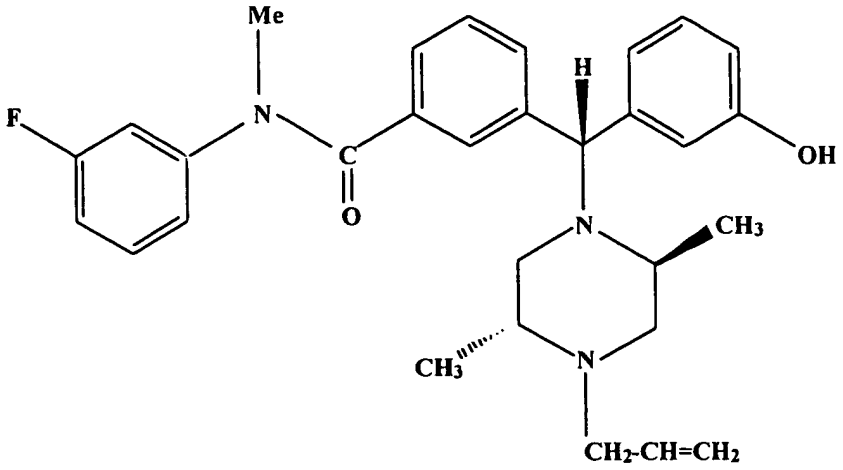
[Fig. 1 shows] Figures 1A and 1B show the effect of the positive isomer of the delta agonist BW373U86 on analgesia and respiratory depression induced by the mu agonist, alfenta. (+)373U86 blocks the respiratory depression (as shown by Fig. 1A), but not the analgesia induced by alfenta (as shown by Fig. 1B). The negative isomer of 373U86 does not have any significant effects on alfenta-induced respiratory depression (data not shown). All doses of BW373U86 are plotted in the analgesia graph, however some points cannot be seen because the symbols are overlapping.

4. On page 66, the paragraph beginning at line 16 has been changed, as follows:

Analgesia was also assessed with a tail-pinch method at the same time points that blood was drawn. Most importantly, BW373U86 did not significantly affect the analgesia produced by alfenta [(Fig. 1, bottom panel)] (Fig. 1B). Overall, the data indicate that BW373U86, or other delta agonists, are useful clinically in intraoperative, postoperative and chronic pain applications to attenuate the respiratory depression and maintain the analgesic effects of mu opioid receptor analgesics.

5 On page 67, the paragraph beginning at line 1 has been changed, as follows:

Both fentanyl (a strong mu-receptor analgesic agent) and 3290W93 (a compound with mixed delta and mu receptor activity), whose chemical structure is shown below:



were found to produce high levels of analgesia. Results are depicted in [Fig. 2] Figures 2A and 2B.

6. On page 67, the paragraph beginning at line 8 has been changed, as follows:

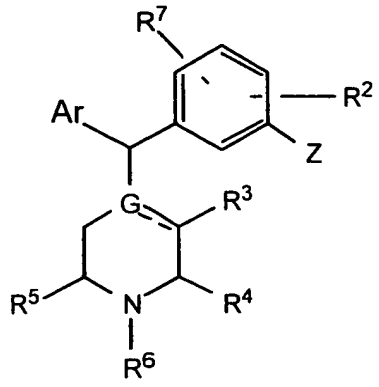
[Fig. 2 shows] Figures 2A and 2B show comparative analgesic and respiratory depression effects of 3290W93 and fentanyl in rats. Effects are plotted at 4 [(top panel)] (Fig. 2A) and 8 [(bottom panel)] (Fig. 2B) minute time points at which peak effects were observed following drug administration. A greater separation between analgesic and respiratory depressant effects occurred following 3290W93 administration than was observed following fentanyl administration.

APPENDIX B

Version with Markings to Show Changes Made in the Abstract

ABSTRACT OF DISCLOSURE

A method of reducing, treating or preventing drug-mediated respiratory depression, muscle rigidity, or nausea/vomiting in an animal, incident to the administration to said animal of a mixed delta/mu opioid agonist or a respiratory depression-mediating drug, comprising administering to the animal receiving said drug an effective amount of a delta receptor agonist compound. [The delta agonist compound may comprise a compound of the formula:



(I)

wherein:

Ar is a 5- or 6-member carbocyclic or heterocyclic aromatic ring with atoms selected from the group consisting of carbon, nitrogen, oxygen and sulfur, and having on a first carbon atom thereof a substituent Y and on a second ring carbon thereof a substituent R^1,

Y is selected from the group consisting of:

hydrogen;

halogen;

C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl;

C_1-C_6 haloalkyl;

C_1-C_6 alkoxy;

C_3-C_6 cycloalkoxy;

sulfides of the formula SR^8 where R^8 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, arylalkyl having a C_5-C_{10} aryl moiety and an C_1-C_6 alkyl moiety, or C_5-C_{10} aryl;

sulfoxides of the formula SOR^8 where R^8 is the same as above;

sulfones of the formula SO_2R^8 where R^8 is the same as above;

nitrile;

C_1-C_6 acyl;

alkoxycarbonylamino (carbamoyl) of the formula $NHCO_2R^8$ where R^8 is the same as above;

carboxylic acid, or an ester, amide, or salt thereof;

aminomethyl of the formula $CH_2NR^9R^{10}$ where R^9 and R^{10} may be the same or different, and may be hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_2-C_6 hydroxyalkyl, C_2-C_6 methoxyalkyl, C_3-C_6 cycloalkyl, or C_5-C_{10} aryl, or R^9 and R^{10} together may form a ring of 5 or 6 atoms, the ring atoms selected from the group consisting of N and C;

carboxamides of the formula $CONR^9R^{10}$ where R^9 and R^{10} are the same as above, or C_2-C_{30} peptide conjugates thereof; and

sulfonamides of the formula $SO_2NR^9R^{10}$ where R^9 and R^{10} are the same as above;

Z is selected from the group consisting of:

hydroxyl, and esters thereof;

hydroxymethyl, and esters thereof; and

amino, and carboxamides and sulfonamides thereof;

G is carbon or nitrogen;

R^1 is hydrogen, halogen, or C_1-C_4 alkyl, C_2-C_4 alkenyl, C_1-C_4 alkynyl;

R^2 is hydrogen, halogen, or C_1-C_4 alkyl, C_2-C_4 alkenyl, C_1-C_4 alkynyl;

R^3, R^4 and R^5 may be the same or different, and are independently selected from hydrogen and methyl, and wherein at least one of R^3, R^4 or R^5 is not hydrogen, subject to the proviso that the total number of

methyl groups does not exceed two, or any two of R^3, R^4 and R^5 together may form a bridge of 1 to 3 carbon atoms;

R^6 is selected from the group consisting of:

hydrogen;

C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl;

C_3-C_6 cycloalkyl;

arylalkyl having C_5-C_{10} aryl and C_1-C_6 alkyl moieties;

alkoxyalkyl having C_1-C_4 alkoxy and C_1-C_4 alkyl moieties;

C_2-C_4 cyanoalkyl;

C_2-C_4 hydroxyalkyl;

aminocarbonylalkyl having a C_1-C_4 alkyl moiety; and

$R^{12}COR^{13}$, where R^{12} is C_1-C_4 alkylene, and R^{13} is C_1-C_4 alkyl or C_1-C_4 alkoxy; and

R^7 is hydrogen or fluorine,

or a pharmaceutically acceptable ester or salt thereof.] Preferred examples of such delta receptor agonist compound include diarylmethyl piperazine compounds and diarylmethyl piperidine compounds, and pharmaceutical compositions thereof, having utility in medical therapy for reducing respiratory depression associated with certain analgesics, such as mu opiates.

APPENDIX C

Clean Copy of the Abstract as Amended

ABSTRACT OF DISCLOSURE

A method of reducing, treating or preventing drug-mediated respiratory depression, muscle rigidity, or nausea/vomiting in an animal, incident to the administration to said animal of a mixed delta/mu opioid agonist or a respiratory depression-mediating drug, comprising administering to the animal receiving said drug an effective amount of a delta receptor agonist compound. Preferred examples of such delta receptor agonist compound include diarylmethyl piperazine compounds and diarylmethyl piperidine compounds, and pharmaceutical compositions thereof, having utility in medical therapy for reducing respiratory depression associated with certain analgesics, such as mu opiates.